

INTRAVENOUS IMMUNOGLOBULIN

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ABSTRACT

There has been a rapid expansion of the use of intravenous immunoglobulin (IVIG) for an ever-growing number of conditions. IVIG is used at a 'replacement dose' (400-600 mg/kg/month) in antibody deficiencies. In contrast it is used at a high dose (2 g/kg/month) as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders. The limitations for IVIG are the cost of the preparation and the need for intravenous infusions. Due to the cost, shortages and growing use of IVIG there have been attempts to develop evidence-based guidelines for the use of IVIG in a wide variety of haematological, autoimmune and neurological conditions. This commentary provides the recommendations and recent publication regarding the use of IVIG in various conditions. Although IVIG is a safe treatment option when compared with other immunosuppressive agents there needs to be an understanding of the potential adverse reactions and their management. It is important for the physician to carefully assess and monitor patients on IVIG so that treatment can be optimised.

INTRODUCTION

Intravenous immunoglobulin (IVIG) replacement therapy has greatly reduced the morbidity due to bacterial infections associated with major forms of antibody deficiency. IVIG has a few proven indications and many potential ones. There has been a rapid expansion in the use of IVIG. It has had a major impact in the treatment of conditions in the fields of neurology, haematology, rheumatology and dermatology. In a recent study in Canada the leading indications for IVIG use were idiopathic thrombocytopenic purpura (17.3%), primary immune deficiency conditions (14.9%) and chronic demyelinating polyneuropathy (11.8%). The leading prescribing specialists were neurologists (32.2%) and haematologists (26.1%).¹ It is safe and does not have the side-effects of steroids or other immunosuppressive agents.

BACKGROUND

Immunoglobulin replacement has been standard therapy for patients with primary immune deficiency diseases since its use by Bruton in 1952.² For many years, these preparations could only be given intramuscularly. Administration of intramuscular immune serum globulin resulted in a decrease in the incidence of infections of patients with agammaglobulinaemia. However injections were painful, the IgG was absorbed slowly and it

was difficult to maintain IgG levels above 2 g/l. Intravenous administration of immune serum globulin caused shock-like episodes, chills and hyperpyrexia. Although attempts were made to modify immune serum globulin for intravenous use, intramuscular use remained the sole form of replacement therapy until 1981 (29 years later) when intravenous preparations became commercially available. This reduced the pain of administration and allowed larger volumes to be infused. Over 25 IVIG preparations are available worldwide which have been approved by various regulatory bodies.³ All are tolerated and effective. The various IVIG products differ in a number of ways including immunoglobulin and IgG subclass distribution, antibody content, approved maximum infusion rate and side-effects. The characteristics of the various products may result in differences in efficacy and safety which may have a significant impact on the choice of product for some patients.

PRODUCTION

An ideal IVIG preparation would contain structurally and functionally intact immunoglobulin molecules with a normal biological half-life and a normal proportion of IgG subclasses. The preparation should contain high levels of antibody or antibodies relevant to its proposed use. There should be no contamination and vasomotor peptides, endotoxin or infectious agents.

Nearly all IVIG preparations are isolated from pooled human plasma (1 000 to 10 000 donors) by the Cohn alcohol fractionation method which results in five plasma fractions. The Cohn fraction II contains the bulk of the antibodies and is appropriate for intramuscular and subcutaneous use. This fraction is further purified for the production of IVIG. The WHO has established the following production criteria for IVIG (1982):⁴

1. Each lot should be derived from plasma pooled from at least 1 000 donors.
2. It should contain at least 90% intact IgG with the subclasses present in ratios similar to normal pooled plasma.
3. IgG molecules should maintain biological activity such as complement fixation.
4. It should be free from contaminants of prekallikrein activator kinins, plasma proteases and preservatives.
5. It should be free from infectious agents.

As for all blood products donors are screened for hepatitis B surface antigen, HIV -p24 antigen, and antibodies to syphilis, HIV-1, HIV-2 and hepatitis C.

Commercial lots are produced from plasma pooled from 1 000 to 10 000 donors so contain a broad spectrum of antibodies. Differences in the manufacturing processes of different IVIG preparations affect opsonic activity, Fc-receptor function and complement fixation. Thus different IVIG preparations should not be considered as a generic product

MECHANISM OF ACTION OF IVIG

IVIG acts via a variety of mechanisms in different disease states and these have been reviewed in detail by Ballou⁵ and Jolles *et al.*⁶ The mechanisms of action of

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therapeutic IVIG are complex. In many conditions advances in the understanding of its actions have been made. The predominant mechanisms depend on both the IVIG dose and on the pathogenesis of the underlying disease and can be divided into four broad groups:⁶

1. Actions mediated via the variable regions F (ab').²
2. Actions of Fc region on a range of receptors.
3. Actions mediated by complement binding within the Fc fragment.
4. Immunomodulatory substances other than antibody in the IVIG preparations

USES OF IVIG

IVIG has many uses and is an important treatment in many diseases. The original use was as replacement therapy (400-600 mg/kg/month) in primary and secondary antibody deficiencies. However, IVIG has many immunomodulatory and anti-inflammatory effects at higher doses (2 g/kg/d) and now more than 100 inflammatory and autoimmune disorders are treated with IVIG. Several IVIG preparations are available and are supplied in either a lyophilised form or as ready-to-use solutions.

IVIG therapy has a few proven indications and many potential ones. There are currently six clinical indications in the USA with Food and Drug Administration (FDA) approval⁷ (Table I):

1. Treatment of primary immunodeficiencies.
2. Prevention of bacterial infections in patients with hypogammaglobulinaemia and recurrent infection caused by B-cell chronic lymphocytic leukaemia.
3. Prevention of coronary artery aneurysms in Kawasaki disease.
4. Prevention of infections, pneumonia and acute graft-versus-host disease (GVHD) after bone marrow transplantation.
5. Reduction of serious bacterial infection in children with HIV.
6. Increase of platelet count in idiopathic thrombocytopenic purpura to prevent or control bleeding.

There are many disorders for which IVIG is used as a

treatment (Table II) and there are several excellent recent reviews on the topic which detail the evidence for the use of IVIG treatment in a wide variety of haematological, autoimmune and neurological conditions.⁶⁻¹⁰

Primary and secondary immunodeficiency

The clearest indication for immune globulin replacement is antibody deficiency. Such deficiencies range from virtually complete absence of all major immunoglobulin classes to more selective deficiencies. The use of IVIG in primary and secondary antibody deficiencies has been thoroughly reviewed by Stiehm.¹¹ Patients with primary antibody deficiencies are susceptible to bacterial infections and require lifelong immunoglobulin replacement therapy. In primary or secondary hypogammaglobulinaemia IVIG protects against infection by providing an adequate concentration of IgG (Table II).^{7,11}

Dosage of IVIG in primary antibody deficiencies

The usual dose of IVIG for antibody replacement is between 400-600 mg/kg every 2-4 weeks. The dose is adjusted so that the trough level just before the next infusion is at least 500 mg/dl. For other uses the doses range between 400 mg/kg/day for 5 days or a more rapid course of 1-2 g/kg given over 1-2 days.⁷

Infusions are given every 3 to 4 weeks at an initial dose of 400-600 mg/kg titrating the dose and interval to achieve a trough level greater than 500 mg/dl in agammaglobulinaemic patients.⁷ The dose of IVIG needed to keep the patient symptom-free depends on the severity of the antibody defect and the catabolic rate of infused IVIG. Doses of 400 mg/kg or greater have improved efficacy over lower doses in reducing the incidence of infection.¹² After the sixth infusion a steady state will have been achieved and the dose or dosing interval should be altered to achieve the optimal clinical result. When IgG production is deficient but not completely absent, such as in CVID, dosing is more complex. IgG trough levels can be unreliable and should not be used as a primary endpoint for guiding

Table I. FDA-approved indications for IVIG

Disease state	Indication
Primary immunodeficiency disease or primary humoral immunodeficiency	Indicated for the treatment of primary immunodeficiency states or for increase of circulating antibody levels in primary immunodeficiency diseases or for replacement therapy of primary immunodeficiency states in which severe impairment of antibody-forming capacity has been shown
Idiopathic thrombocytopenic purpura (ITP)	Indicated when a rapid increase in platelet count is needed to prevent bleeding, control bleeding, or both in ITP or to allow a patient with ITP to undergo surgery
Kawasaki disease (syndrome)	Indication for the prevention of coronary artery aneurysms associated with Kawasaki disease
B-cell chronic lymphocytic leukaemia	Indicated for the prevention of bacterial infections in patients with hypogammaglobulinaemia, recurrent bacterial infections, or both, associated with B-cell chronic lymphocytic leukaemia
HIV infection	Indicated for paediatric patients with HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalisation and increase time free of serious bacterial infection
Bone marrow transplantation	Indicated for bone marrow transplant recipients ≥ 20 years of age to decrease the risk of septicaemia and other infections, interstitial pneumonia of infections or idiopathic causes, and acute GVHD in the first 100 days after transplantation

Adapted from Orange *et al.*⁷

Table II. Major uses of IVIG

Neurology	Haematology	Immunology	Dermatology	Other
Guillain Barre syndrome	Immune thrombocytopenia	Primary antibody deficiencies (XLA, CVID, HIGM WAS and others)	Kawasaki syndrome	Vasculitis
Multifocal motor neuropathy	Post bone marrow transplant	Secondary antibody deficiencies (myeloma, CLL, drugs and other causes)	Dermatomyositis	Systemic lupus erythematosus
Chronic inflammatory demyelinating polyneuropathy	Myeloma and chronic lymphocytic leukaemia		Toxic epidermal necrolysis	Streptococcal toxic shock syndrome
Dermatomyositis and inflammatory myopathies	Parvovirus B19-associated aplasia		Blistering diseases	Birdshot retinochoroidopathy
Myasthenia gravis	Immune neutropenia		Immune urticaria	Autoimmune uveitis
Lambert-Eaton syndrome	Immune haemolytic anaemia		Atopic dermatitis	Mucous membrane pemphigoid
Stiff person syndrome			Scleromyxoedema	
			Pyoderma gangrenosum	

IVIG is used mainly at high dose (2 g/kg) for the indications listed in neurology, haematology, rheumatology, dermatology and others while in immunology replacement doses (0.4 g/kg) are given. XLA – X-linked agammaglobulinaemia, CVID – common variable immunodeficiency, HIGM- immunodeficiency with hyper-IgM, WAS – Wiskott Aldrich syndrome, CLL – chronic lymphocytic leukaemia.

Adapted from Jolles *et al.*⁶

therapy. A target trough level of a serum IgG equal to the pretreatment level plus 300 mg/dl has been used. A dose must be individualised and titrated to achieve clinical effect for each patient. The issue of IgG dose for patients with normal IgG levels but impaired specific antibody production is more difficult because IgG trough levels are not particularly useful. Dose adjustments will be needed with children's growth or in protein-losing conditions. Despite the number of studies comparing different IgG doses of primary immunodeficiency, none has directly compared different dosing intervals. At present the dosing interval should be selected according to the ability of a given regimen to maintain an adequate IgG trough level, an acceptable clinical effect, or both. If patients who are receiving IVIG every 28 days experience malaise or upper respiratory tract symptoms in the week before infusion, a more frequent dosing schedule should be considered.

Monitoring IVIG in primary antibody deficiencies

The therapeutic guidelines for the monitoring of the use of IVIG in primary antibody deficiencies are summarised in Table III.

Monitoring IVIG therapy

IVIG therapy can take up to 6 months to achieve maximal benefits. Trough levels increase gradually with optimal dosing (400-600 mg/kg/month) until a steady state is achieved after 4-8 months of regular IVIG infusions. Because of individual variation in IgG distribution and catabolism, serum IgG trough levels (i.e. prior to infusion level) should be checked every 2 months for the first 8 months of therapy to ensure that target trough levels of > 500 mg/dl are met or exceeded. Once the dose has been optimised, trough levels need only be monitored every 6 months.¹¹

Monitoring liver function

Liver function including serum transaminase levels should be monitored regularly (every 3 months) to exclude subclinical, passively transmitted hepatitis.

Batch numbers of the IVIG infused must be recorded in the patient notes.

Monitoring infections

While patients are on IVIG therapy it is advised that the number, duration, site and severity of all infections, all antibiotic use and other relevant clinical details be recorded to document the benefit of the IVIG therapy.

Monitoring disease progression

Chest damage may progress insidiously despite optimal IVIG therapy so regular review of pulmonary function is recommended.

Autoimmune diseases

High dose IVIG has immunosuppressive and anti-inflammatory effects and has been used with variable results in several systemic autoimmune diseases (Table II).^{6,7} In contrast to the 'replacement' dose of 400 mg/kg/month, the 'high' dose IVIG is given at 2 g/kg/month when it is used as an immunomodulatory agent in immune or inflammatory disorders.

Idiopathic thrombocytopenic purpura (ITP)

ITP is an FDA-approved indication for IVIG. It is an important treatment option of acute ITP in children with the severe presentation (platelet count < 20 x 10⁹/l) of this disorder.⁸ It is used to treat patients at greatest risk of bleeding complications or those with chronic refractory disease. The mechanism of action is thought to be blockade of the Fc receptors in the reticuloendothelial system leading to inhibition of binding and destruction of antibody-coated platelets.

Haematological disorders

IVIG has been used in numerous haematological conditions (Table II).^{6,7}

Treatment for haemolytic disease of the newborn (HDN) includes phototherapy and exchange transfusion.

TABLE III. Recommendations for the use of IVIG in primary antibody immunodeficiencies

1. Record brand, lot number, dose, infusion rate, and side reactions
2. Maintain the IgG trough levels > 500 mg/dl
3. IgG trough levels gradually increase for 4-8 months on high dose IVIG therapy
4. For every 100 mg/kg of IVIG given, IgG peak levels increase 200-250 mg/dl and trough levels increase 100 mg/dl (after 28 days)
5. Usual maintenance dose is 400-500 mg/kg every 4 weeks
6. Check IgG trough level every 2 months until stable, then every 6 months
7. Check blood count and liver function tests twice yearly
8. IgG half-life varies in different patients so dosage must be individualised
9. Consider extra doses with infection, stress and gastrointestinal or genitourinary loss
10. Home infusions, slow subcutaneous infusions and rapid infusion of 10-12% IVIG can be used for convenience, economy and shortened administration time in some patients

Adapted from Stiehm.¹¹

sion. In the last few years IVIG has been shown to significantly reduce the overall use of exchange transfusion.^{13,14} IVIG is recommended for the treatment of HDN with severe hyperbilirubinaemia. The American Academy of Pediatrics (2004)¹⁵ recommends IVIG treatment (0.5-1.0 g/kg over 2 hours) if the bilirubin is rising despite intensive phototherapy or if it is within 2-3 mg/dl (34-51 $\mu\text{mol/l}$) of the threshold for exchange transfusion.^{8,15} The mechanism of action is uncertain but IVIG is thought to inhibit haemolysis by blocking antibody receptors on red blood cells.

Neurological disorders

IVIG is licensed for use in Guillain Barre syndrome (GBS) but is used in many other neurological conditions (Table II).^{7,9,10,16} A Cochrane systematic review has shown that IVIG is as efficacious as plasma exchange in GBS.¹⁷ There are no randomised trials of IVIG in children with GBS but the evidence from the adult trials has been sufficient for IVIG to be recommended in children with GBS. IVIG (2 g/kg over 2-5 days for adults, 2 days for children) is recommended as a treatment for GBS within 2 weeks of symptom onset for: (i) patients with grade 3 symptoms (able to walk with aid) or greater; or (ii) patients with symptoms that are progressing.

ROUTE OF ADMINISTRATION

Immunoglobulin replacement therapy can be given via the intramuscular, subcutaneous and intravenous routes. Preparations intended for the intramuscular and subcutaneous routes must not be given intravenously. Intravenous administration pooled human immunoglobulin has been available from 1981 and has become an important therapy in clinical medicine. IVIG has allowed infusion of higher doses over a short time, and has remained the standard route of administration. However IVIG therapy is not ideal for all patients. The limitations of IVIG are:

- Difficulty for those with poor venous access
- Patients with recurrent systemic reactions
- Requires hospitalisation or a good home-care programme.

Subcutaneous immunoglobulin (SCIg)

Subcutaneous administration of immunoglobulin by slow infusion was tried in the late 1970s.¹⁸ It was abandoned

because of the length of time of administration and the occurrence of sterile abscesses.

However more recently reports have shown that rapid subcutaneous immunoglobulin (SCIg) therapy is a safe, effective and well-tolerated alternative to IVIG.^{19,20,21} SCIg treatment does not require venous access and is associated with the slow release of IgG into the blood which enables trough IgG levels to remain high and stable between infusions.^{22,23} The growing availability of SCIg therapy for home administration has offered increased flexibility to both children and adults.^{21,24} There are no significant differences in efficacy or adverse reaction results between immunoglobulin replacement therapy given subcutaneously and intravenously.^{21,25} There has been an increase in use of the subcutaneous route in Europe. The immunoglobulin dose used for subcutaneous replacement therapy is usually 0.1 g/kg/week.

Subcutaneous infusions are only indicated in primary immunodeficiency disorders. It is unclear whether subcutaneous infusions will be effective for disorders depending on the immunomodulatory action of IVIG and it is not recommended for this use.

SAFETY OF IVIG

Systemic reactions to IVIG infusion range from 3% to 15%. They are usually self-limiting and can be avoided by decreasing the rate of the infusion. Infusion rates are usually started at 0.01-0.02 ml/kg/min and increased up to 0.1 ml/kg/min. Fortunately most IVIG reactions are mild and non-anaphylactoid. Typically they include backache, abdominal pain, nausea, chills, rhinitis, asthma, low-grade fever, myalgia and headaches (Table IV). Slowing or stopping the infusion for 15-30 minutes will reverse many reactions. Pretreatment prophylaxis with diphenhydramine (1 mg/kg/dose), acetaminophen (15 mg/kg/dose), aspirin (15 mg/kg/dose) or ibuprofen (5 mg/kg/dose) is also helpful. More serious reactions can be treated with hydrocortisone (6 mg/kg/dose; maximum 100 mg).¹¹

More serious adverse events can occur during or soon after infusion: anaphylaxis, renal, cardiovascular, central nervous system and haematological events have been reported.²⁶ Anaphylaxis is very rare and is associated with anti-IgA antibodies in some patients with total IgA deficiency (IgA < 0.05 g/l). Acute renal failure and neurodegeneration have been associated with IVIG but not temporally related to the infusion.⁷ It has been suggested that the sucrose-based products are

Table IV. Adverse effects of IVIG therapy

Immediate infusion-related*	Transmission of infective agents*	Consequences of increasing serum IgG [†]
Mild to moderate reactions – headaches, backache, chills, nausea, muscle pain – occur in approximately 1% of infusions and are largely rate-related	Hepatitis C – several outbreaks to date; additional anti-viral step introduced by most manufacturers following last outbreak in 1994	Renal – reversible renal impairment (majority of cases), acute renal failure in mixed cryoglobulinaemia
Severe – anaphylaxis may occur very rarely in IVIG recipients who have high titres of anti-IgA antibodies	? Prions – potential risk; no documented cases to date	Haematological – cerebral and coronary thromboses, acute haemolysis, neutropenia Neurological – acute aseptic meningitis Dermatological – eczema, urticaria, erythema multiforme cutaneous vasculitis

*May occur with either low or high-dose IVIG; [†]predominantly associated with high-dose IVIG.
Adapted from Jolles *et al.*⁶

more commonly associated with acute renal failure. The more important and commonly seen IVIG-induced adverse effects are summarised in Table IV.

The risk of infectious complications is low. There are stringent requirements for donor screening and transmissible disease testing. The manufacturing process includes steps of viral inactivation or removal to protect against infectious agents that might be present despite screening procedures. Hepatitis B and HIV have never been transmitted through IVIG and there is no known case of transmission of Creutzfeldt-Jakob disease. Since 1984 transmission of hepatitis C has been reported 10 times and is estimated to have involved 4 000 patients worldwide.³ Further antiviral steps of pasteurisation, nanofiltration or solvent detergent treatment have been added to the manufacturing procedures to decrease this risk.

IVIG is a product made from large pools of human plasma and thus infectious disease transmission always remains a possibility. The risk of infection from human plasma preparations can never be completely ruled out.

The effect of live vaccines may be inhibited if IVIG is used. It is recommended that these vaccines be given 3 months after the last dose of IVIG.

COST OF IVIG

In 1997 there was a worldwide shortage of IVIG due to disruption of production caused by the need for US-based plasma fractionators to comply with more stringent US FDA requirements. Intravenous immune globulin costs between R220 and R350 per gram (depending on quantity bottled) (Table V). These costs do not include the costs associated with administration of IVIG.

CONSIDERATIONS IN THE USE OF IVIG

Because of the cost, shortages and growing use of IVIG there have been attempts in many countries to develop guidelines for monitoring of and indications for the use of IVIG.^{1,7,10,27} Clinicians should limit their prescription of IVIG to conditions for which efficacy is

Table V. Costs of IVIG in South Africa (December 2007)

Patient	Schedule	Cost of IVIG	
		0.5 g/kg	2.0 g/kg
20 kg child	1 dose	R 2 853	R 9 098
	1x monthly/yr	R 37 089	R 118 274
	1x 3-weekly/yr	R 48 501	R 154 666
70 kg adult	1 dose	R 8 000	R 31 000
	1x monthly/yr	R 104 000	R 403 000
	1x 3-weekly/yr	R 136 000	R 527 000

supported by evidence-based studies. In South Africa it must be ensured that the patients who will benefit most from IVIG (determined from evidence-based guidelines) will have access to this treatment. It is important to recognise that IVIG products vary in their composition and these differences have clinical implications particularly when used for immunomodulation.²⁸

Although there is statutory documentation for the use of blood, there are no guidelines for the use or monitoring of IVIG in South Africa although it has been recognised that this would be valuable. It is advised that clinicians:

- Document product, lot number and dose of immunoglobulin used in patients
- Document the indication for the IVIG
- Monitor liver function tests and viral screens, pre-therapy and serially throughout IVIG therapy
- Record any side-effects.

Declaration of conflict of interest

The author declares no conflict of interest.

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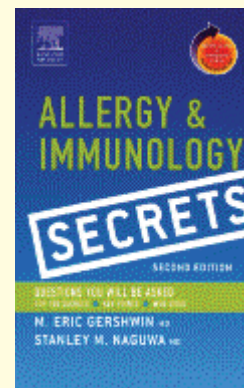
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